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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,823	02/12/2002	Waldemar Debinski	6460-41	8785

7590 10/27/2005

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,823	DEBINSKI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-43* is/are pending in the application.

4a) Of the above claim(s) *2-8 and 19-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/16/05 has been entered.

2. Claims 1-10 and 12-43 are pending.

3. Claims 2-8 and 19-43 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 9-10, and 12-18, drawn to a method for detecting a cancer in a brain tissue for a VEGF-D protein marker using a probe wherein the probe is a VEGF-D antibody, are being acted upon in this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 9-10, and 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for diagnosing glioblastoma multipforme, the method comprising the steps of: (A) providing the brain tissue sample, (B) contacting the brain tissue with a labeled antibody that binds specifically to human VEGF-D protein, a native human VEGF-D protein or a homology domain of human VEGF-D and (C) analyzing the brain tissue for overexpression of VEGF-D, as compared to normal brain tissue, (2) the said method wherein the brain tissue sample comprises cell exhibiting abnormal ploidy for chromosome X, and (3) the said method wherein the antibody is monoclonal antibody or polyclonal antibody, **does not** reasonably provide enablement for any method for detecting any cancer in any brain tissue sample, the method comprising the steps of (A) providing the brain tissue sample; (B) analyzing the brain tissue sample for overexpression of any "VEGF-D marker", as compared to

normal brain tissue, (2) the said method wherein the VEGF-D marker is any VEGF-D protein, any native VEGF-D protein, any proteolytic cleavage product of any VEGF-D precursor protein and consists of any VEGF-D homology domain, (3) the method mentioned above wherein the step (A) of providing a brain tissue sample comprises obtaining the brain tissue sample from a human subject; and the step (B) of analyzing the brain tissue sample comprising cells exhibiting abnormal ploidy for chromosome X by contacting the brain tissue sample with any probe that specifically binds to any VEGF-D protein, any probe comprises a detectable label that specifically binds to any VEGF-D protein, any probe comprises any antibody, any polyclonal antibody, any monoclonal antibody, any anti-VEGF-D homology domain antibody as set forth in claims 1, 9-10, and 12-18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of diagnosing glioblastoma multipforme by detecting the overexpresssion of VEGF-D in the human brain tissue as compared to normal brain tissue using only monoclonal antibody VD1 that binds specifically to human VEGF-D (page 36) or the homology domain of human VEGF-D (page 18). The specification further discloses the method wherein the antibody could be a polyclonal or binding fragment thereof that binds specifically to VHD of human VEGF-D.

The specification does not teach how to make any and all "probe", and antibody that binds to any and all VEGF-D for the claimed method. This is because there is insufficient guidance as to the structure of the probe without the amino acid sequence or nucleic acid sequence of the probe. Further, there is insufficient guidance as to the binding specificity of all antibodies that bind to all VEGF-D, and any VEGF-D homology domain. The specification does

not disclose whether the antibody or probe binds to other VEGF-D. The specification is silent whether other forms of brain cancer are associated with overexpression of VEGF-D.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Given the unlimited number of undisclosed VEGF-D as well as probes and antibodies that bind to any VEGF-D, it is unpredictable which undisclosed probes or antibody will be specific for human VEGF-D, in turn, would be useful for detecting any brain cancer in all mammal and brain cancer such as human glioblastoma multipforme. Until the structure of the other VEGF-D or the probes have been taught, and that all other brain cancers are associated with overexpresssion of VEGF-D, it would take undue amount of experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

7. Claims 1, 9-10, and 12-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any and all probe, and any and all antibody that binds to any VEGF-D, any native VEGF-D protein, any proteolytic

product of any VEGF-D precursor protein consists of any VEGF-D homology domain for the claimed method of detecting any and all cancer in any brain tissue.

The specification discloses only a method of diagnosing glioblastoma multipforme by detecting the overexpresssion of VEGF-D in the human brain tissue as compared to normal brain tissue using only monoclonal antibody VD1 that binds specifically to human VEGF-D (page 36) or the homology domain of human VEGF-D (page 18). The specification further discloses the method wherein the antibody could be a polyclonal or binding fragment thereof that binds specifically to VHD of human VEGF-D.

With the exception of the specific antibody that binds specifically to human VEGF-D for diagnosing glioblastoma multipforme in human tissue sample, there is insufficient written description about the structure associated with function of all probes for the claimed method. Further, there is inadequate written description about the binding specificity of all antibodies that bind to any and all VEGF-D, including any VEGF-D homology domain.

The specification discloses only one antibody that binds specifically to human VEGF-D or the human VEGF-D homology domain for detecting only glioblastoma multipforme, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of antibody, and probe that bind to all VEGF-D to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001:

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1, 9-10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: contacting the tissue sample with a labeled antibody that binds specifically to human VEGF-D.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 9 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,235,713 B1 (of record, filed Aug 1997; PTO 892) in view of US Pat No. 5,874,290 (of record, Feb 1999; PTO 892) and Hamel et al (Acta Neurochirugica 142: 113-138, 2000; PTO 892).

The '713 patent teaches a method of detecting VEGF-D in a biological sample comprising the steps of contacting the sample with a probe such as monoclonal and polyclonal antibody that bind specifically to VEGF-D and detecting the binding by means of a detectable label (see col. 6, lines 66-67 bridging col. 7, lines 1-7, col. 5, lines 51-67, in particular). The reference VEGF-D is a native VEGF-D protein (see col. 19, lines 34-42, VEGFD full FLAG, in particular) and proteolytic cleaves to produce product comprises a VEGF-D homology domain (see col. 19, line 25, VEGFDΔNΔC, in particular). The '713 paten teaches VEGF-D is located on the X chromosome in band p22.1 (see col. 24, lines 1-8, in particular) and is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the method for detecting a cancer in a brain tissue sample instead of any biological sample.

The invention in claim 9 differs from the teachings of the reference only in that the method for detecting a cancer in a human brain tissue sample instead of any biological sample.

The '290 patent teaches various VEGFs that have been shown to overexpressed in different types of brain tumors (see col. 3, lines 5-14, and references therein, in particular). The '290 patent further teaches the use of fetal brain tissue and cell lines derived from human such as human glioblastoma multiforme tumor tissue for diagnosis of brain tumor using specific VEGF markers (see col. 43, lines 35-62, in particular).

Hamel et al teach gliomas are among the most vascularized tumors in man (see page 121, col. 1, first paragraph, in particular). Hamel et al further teach VEGF is expressed abundantly in high grade gliomas (see page 121, col. 1, first full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to detect overexpression of VEGF-D marker as taught by the '290 patent and Hamel et al using the probe such as the anti-VEGF-D antibody as taught by the '713 patent to human brain tissue derived from human such as human glioblastoma multiforme tumor tissue or biopsy as taught by the '290 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '290 patent teaches various VEGFs have been shown to overexpressed in different types of brain tumors (see co. 3, lines 5-14, and references therein, in particular). Hamel et al teach gliomas are among the most vascularized tumors in man (see page 121, col. 1, first paragraph, in particular). Hamel et al further teach VEGF is expressed abundantly in high grade gliomas (see page 121, col. 1, first full paragraph, in particular). VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk as taught by the '713 patent (see col. 6, lines 16-18, in particular). The recitation of "as compared to normal brain tissue" is within the purview of one ordinary skilled in the art to use the appropriate normal brain tissue as a control to compare the increase or decrease of protein expression in any diagnostic method.

Applicants' arguments filed 9/16/05 have been fully considered but are not found persuasive.

Applicants' position is that Applicants invention is that claims 1, 12 and 18 have been amended to more explicitly describe the claimed invention. The '713 patent does not teach or disclose that VEGF-D is detectable in brain tumors, especially high grade gliomas which are non-metastatic tumors, and detection of over-expressed VEGF-D in brain tissue is not an "indicator of future metastic risk". The VEGF-D peptide discussed in the '713 patent is not a full-length native

protein but a fragment from residue 93 to 201 (see col. 18, lines 66-67). The '290 patent does not teach over expression of VEGF-D in glioblastoma's. The '290 patent does not provide one of ordinary skill in the art any guidance as to which VEGF family, which brain tumor, does over expression of a gene imply over expression of a protein, overexpressed as compared to what? Furthermore, the experimental results do not show that the VEGF2-2 is overexpressed in glioblastoma tumors.

In response, the claims encompass a method of detecting any cancer in any brain tissue sample and analyzing the brain tissue sample for overexpression of any VEGF-D marker such as any VEGF-D nucleic acid or any VEGF-D protein. The claims do not require detection of a full-length VEGF-D protein using the particular anti-VEGF-D antibody. The specification defines VEGF-D marker as any VEGF-D nucleic acid or any VEGF-D protein (page 8, first paragraph).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., glioblastoma) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that the '713 patent fails to teach the full length native protein, none of the claims recite VEGF-D protein is a *full length* VEGF-D protein.

13. Claims 10, 12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,235,713 B1 (of record, filed Aug 1997; PTO 892) in view of US Pat No. 5,874,290 (of record, Feb 1999; PTO 892) and Hamel et al (Acta Neurochirugica 142: 113-138, 2000; PTO 892) as applied to claims 1, 9 and 13-17 mentioned above and further in view of Stacker et al (of record, J. Biol. Chem. 274(45): 32127-32136; Nov 1999; PTO 1449) and Achen et al (of record, Eur. J. Biochem. 267: 2505-2515, May 2000; PTO 1449).

The combined teachings of the '713 patent, the '290 patent and Hamel et al have been discussed supra.

The invention in claim 10 differs from the combined teachings of the references only in that the method for detecting a cancer in a brain tissue sample wherein the VEGF-D protein is a native VEGF-D protein.

The invention in claim 12 differs from the combined teachings of the references only in that the method for detecting a cancer in a brain tissue sample wherein the VEGF-D protein is

proteolytic cleavage product of a VEGF-D precursor protein and consists of a VEGF-D homology domain.

The invention in claim 18 differs from the combined teachings of the references only in that the method for detecting a cancer in a brain tissue sample wherein the monoclonal antibody is an anti-VEGF-D homology domain antibody. .

Stacker et al teach VEGF-D is proteolytically processed to generate a bioactive fragment such as VEGF-D homology domain (VHD) (see page 32128, col. 1, first full paragraph, Figure 1, in particular). Stacker et al further teach polyclonal antibody that binds specifically to VEGF-D homology domain (VHD) (see page 32128, Antisera, in particular).

Achen et al teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that bind specifically to VEGF-D homology domain (see page 2507, col. 2, Results, production of anti-VEGF-D mAbs, page 2508, col. 2, last paragraph, in particular). Achen et al teach antibody such as VD2 also binds to the native VEGF-D protein (see page 2508, col. 2, in particular) and the VEGF-D homology domain (see page 2511, col. 1, in particular). Achen et al teach the reference antibody could block the mitogenic response of vascular endothelial cells to VEGF-D (see page 2512, col. 1, in particular) and strongly inhibits the binding of VEGFDΔNΔC or the VEGF-D homology domain (VHD) to both VEGFR2 and VEGFR3 (see page 2511, col. 1, last par, in particular). Achen et al teach that these antibodies are useful for analyzing angiogenesis induced by VEGF-D and its contribution to metastatic spread (see page 2513, col. 1, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the VEGF-D specific antibody as taught by the '713 patent for the VD2 monoclonal antibody that binds specifically to the native and/or VEGF-D homology domain (VHD) as taught by Achen et al or the polyclonal antibody that binds specifically to the VEGF-D homology domain (VHD) as taught by Stacker et al since the VEGF-D homology domain (VHD) is the active fragment of VEGF-D after proteolytic processing as taught by Stacker et al and Achen et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Stacker et al teach VEGF-D is proteolytically processed to generate a bioactive fragment such as VEGF-D homology domain (VHD) (see page 32128, col. 1, first full paragraph, Figure 1, in particular).

Achen et al teach VD2 monoclonal antibody specific to VHD is useful for analyzing angiogenesis induced by VEGF-D and its contribution to cancer (see page 2513, col. 1, last paragraph, in particular). The '290 patent teaches various VEGF have been shown to overexpressed in different types of brain tumors (see co. 3, lines 5-14, and references therein, in particular). The '713 patent teaches VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens (see col. 6, lines 16-18, in particular).

Applicants' arguments filed 9/16/05 have been fully considered but are not found persuasive.

Applicants' position is that arguments regarding the combined teachings of the '713 and '290 have been discussed. Neither Staker et a1 nor Achen et al. standing alone or in combination teach the detection of a VEGF-D homology domain in brain cancer. Since, a normal brain does not have a lymphatic system and GBM does not grow lymphatic vessel, applicants surprising discovery was the ubiquitous detection of the VEGF-D homology domain in the brain.

In response to applicant's argument that normal brain does not have a lymphatic system and GBM does not grow lymphatic vessel, Hamel et al teach gliomas are among the most vascularized tumors in man (see page 121, col. 1, first paragraph, in particular) and VEGFs are expressed abundantly in high grade gliomas such as GBM (see page 121, col. 1, first full paragraph, in particular). The teachings of Hamel et al and the '290 patent pertaining to the overexpression of VEGFs in brain cancer, the teachings of '713 patent pertaining to VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens, and the teachings of the Achen et al and Stacker et al pertaining to the antibody that binds to native and/or VEGF-D homology domain would have led one of ordinary skill in the art at the time the invention was made to combine the references to detect VEGF-D in cancer of brain tissue using antibody that binds to the native and/or VEGF-D homology domain. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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